Successful treatment of disseminated methicillin-resistant *Staphylococcus aureus* with fosfomycin, cefoperazone/sulbactam and rifampin followed by fusidic acid and rifampin

Few data exist regarding treatment of disseminated methicillin-resistant *Staphylococcus aureus* (MRSA) with fosfomycin and fusidic acid.[1,2] We report the case of an MRSA-associated catheter-related bloodstream infection (CR-BSI) successfully treated with the combination of fosfomycin, cefoperazone/sulbactam and rifampin followed by fusidic acid and rifampin.

A 64 year-old Thai man with type II diabetes, chronic renal failure, idiopathic thrombocytopenic purpura (ITP), and prior anaphylaxis to vancomycin was admitted to Thammasart University Hospital with fever and five days of left knee and right ankle swelling. Two months prior to admission, he underwent subclavian tunneled catheter placement for hemodialysis. On admission, examination revealed a temperature of 38.7 °C, pulse 110/minute, respirations 18/minute, blood pressure 110/70 mmHg, with swelling, erythema, and tenderness of the left knee and right ankle. The leukocyte count was 19.1×10^9/L (94% neutrophils), platelet count 70×10^9/L, blood urea nitrogen 55 mg/dL, serum creatinine 3.6 mg/dL; an HIV antibody test was negative and chest X-ray was normal. Blood cultures were obtained from the tunneled catheter and two peripheral sites. Given thrombocytopenia and prior anaphylaxis to vancomycin, we initially treated with fosfomycin, rifampin and cefoperazone/sulbactam, catheter removal, and drainage of the left knee and right ankle. Four days into therapy, the blood and intraoperative cultures grew MRSA susceptible to vancomycin, fosfomycin, linezolid, fusidic acid, and rifampin and a transesophageal echocardiogram revealed no evidence of valvular vegetation. Susceptibility testing for fosfomycin was performed using agar dilution, as recommended by the manufacturer; a MIC of $\geq$128 mg/L characterizes a strain as resistant, 32–64 mg/L as intermediate, and $\leq$16 mg/L as susceptible.[3,4] After surgical debridement, the patient received a two-week course of fosfomycin, cefoperazone/sulbactam plus rifampin, followed by fusidic acid plus rifampin for another 90 days. Post-treatment surveillance blood cultures were negative and three months post-treatment the patient had full resolution of infection.

Successful treatment of severe MRSA can usually be achieved with vancomycin or linezolid with or without adjuvant oral therapies. In patients with MRSA infection who are allergic to these medications or have thrombocytopenia, the combination of fosfomycin plus beta-lactam and/or rifampin, followed by fusidic acid plus rifampin is an attractive alternative. Fosfomycin is a phosphoenolpyruvate analogue that irreversibly inhibits enolpyruvate transferase resulting in prevention of the formation of *N*-acetyl-muramic acid, the first stage of peptidoglycan synthesis of the bacterial cell wall.[3,5] It is bactericidal with efficacy for MRSA, intermediate glycopeptide-susceptible or -resistant enterococci, and Enterobacteriaciae.[3,5] In vitro data suggest a synergistic effect of fosfomycin and fusidic acid in combination with beta-lactam and/or rifampin.[3] The rationale for these combination therapies are: (1) to extend the antimicrobial spectrum of each agent from that shown when used alone, (2) to potentiate the antibacterial activities of the component agents, (3) to decrease or to prevent the emergence of drug-resistant bacteria, and (4) to reduce potential side-effects of the drugs used.[6,7] Although cefoperazone/sulbactam has limited in vitro activity against MRSA, early in vitro data suggest its combination with fosfomycin is synergistic against MRSA.[6] Our report can be added to the short list of successful treatment regimens against MRSA infection using fosfomycin with beta-lactam and/or rifampin followed by fusidic acid and/or rifampin.[1] Furthermore, our case is the first report of successful treatment of severe disseminated MRSA infection with the combination of fosfomycin with cefoperazone/sulbactam and rifampin followed by fusidic acid and rifampin, as has been supported by evidence from in vitro studies.[3,6]

With the emergence of community-associated MRSA and MRSA with reduced susceptibility to vancomycin, physicians should be aware of alternative treatment strategies especially in patients for whom oxazolidinones and glycopeptides cannot be used. While fusidic acid has not undergone regulatory approval for use in the USA, this regimen is a therapeutic option in Europe, Australia, and most developing countries.[5] Our case supports the benefit of fosfomycin and fusidic acid, in combination with beta-lactam and/or rifampin for treatment of disseminated MRSA infection, and highlights the need for further studies of these combination regimens.

Conflict of interest: No conflict of interest to declare.

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Rapid diagnosis of pneumococcal pneumonia in adults using the Binax NOW *Streptococcus pneumoniae* urinary antigen test

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia (CAP) worldwide and a major cause of morbidity and mortality.[1] *S. pneumoniae* is probably also the leading cause of pneumonia of unknown etiology. The role of microbiological tests is in the detection of an etiologic agent causing infection so that directed therapy is possible. However, the diagnosis of pneumococcal infections relies heavily on culture of *S. pneumoniae* from blood or other normally sterile fluids and is limited by prior administration of antibiotics.[2] For these reasons, causative pathogens may remain unidentified in up to 50% of patients and broad-spectrum antibiotic therapy may be continued unnecessarily for prolonged periods of time.

The recent study by Genne et al. has shown that detection of urinary pneumococcal antigen by using the Binax NOW *S. pneumoniae* antigen test (immunochromatographic test (ICT)) is a useful technique for the rapid diagnosis of pneumococcal infections in adults.[3] We performed a retrospective study to investigate the performance of the ICT by use of selected non-concentrated urine samples from adult CAP patients. Approval to conduct the study was obtained from the St Elisabeth Hospital Ethics Committee.

The CAP patients were included in the study only if a urine sample was obtained within 48 h after hospital admission. The cases were adult patients (>16 years of age) from whom blood cultures grew *S. pneumoniae* ($n = 52$), or patients for whom pneumococcal pneumonia was confirmed with positive sputum culture results ($n = 6$). Controls ($n = 136$) were selected from adult patients presenting with lower respiratory tract infections. A large proportion of the urine samples were obtained from patients with proven legionnaires' disease ($n = 98$) according to criteria used by the European Working Group on Legionella Infections (EWGLI; www.ewgli.org). The laboratory results of the remaining control patients were as follows: *Haemophilus influenzae* ($n = 10$), *Moraxella catarrhalis* ($n = 3$), *Staphylococcus aureus* ($n = 4$), *Escherichia coli* ($n = 2$), *Acinetobacter baumannii* ($n = 1$), *Streptococcus pyogenes* ($n = 2$), *Klebsiella pneumoniae* ($n = 1$), *Mycobacterium tuberculosis* ($n = 3$), *Pneumocystis jirovecii* ($n = 1$). Eleven patients were included who had a four-fold rise or more in complement-fixating antibodies against influenza A virus ($n = 2$), adenovirus ($n = 1$), *Chlamydia psittaci* ($n = 3$), *Mycoplasma pneumoniae* ($n = 4$), and parainfluenza virus ($n = 1$).

Fifty-eight cases (median age 55 years; range 16—85 years) and 136 controls (median age 56 years; range 16—84 years) were included. Pneumococcal urinary antigen was positive (after 15 minutes reading) in 40 of 58 pneumococcal cases and in three of 136 controls, giving a test sensitivity of 69% (95% CI 58—78%) and a test specificity of 98% (95% CI 93—99%) overall. The frequency of antigen detection was greater for bacteremic pneumococcal pneumonia (38/52 (73%)) than for non-bacteremic pneumococcal pneumonia (2/6 (33%)) ($p = 0.07$).

Of the three false-positive results in our study, two occurred in patients who might be considered at high risk for pneumococcal infection. One patient was a 78-year old female admitted to the hospital with renal impairment, malaise, fever, and shortness of breath. Chest radiography showed extensive bilateral consolidation of the lung. Blood cultures remained negative and in a sputum sample *Haemophilus influenzae* was cultured. She died a week after admission to the hospital. The second patient was a 31-year old HIV positive female admitted with a respiratory tract infection and a consolidation on chest radiograph. Blood and sputum cultures were obtained but remained negative. Her condition improved after initiation of amoxicillin therapy (1000 mg iv per 6 hours) and she later showed a four-fold rise in complement-fixating antibodies against influenza A virus. The third patient was a 42-year old female admitted with an acute exacerbation of chronic pulmonary disease and blood cultures yielding *Haemophilus influenzae*. None of these patients had nasopharyngeal swabs taken to detect pneumococcal carriage. It is possible that these patients had co-infection with *S. pneumoniae*.

Although selection bias may possibly have affected our sensitivity and specificity results, our findings indicate that the sensitivity of the test is about 75% when positive blood cultures are used as the 'gold standard'. These findings are similar to those of other investigators who have used the NOW *S. pneumoniae* urinary antigen test. Murdoch et al. studied 420 adults with CAP, including 20 patients with pneumococcal bacteremia, 16 (80%) of whom had detectable urinary antigen levels.[4] In determining the test specificity, Murdoch et al. used 169 adult control patients with an admission diagnosis other than a respiratory or infectious disease and found that none had detectable pneumococcal antigen (specificity 100%). Dominguez et al. detected pneumococcal antigen in urine specimens of 82% of 28 patients with bacteremic pneumococcal pneumonia.[5] The study by Dominguez et al. also used control patients with pneumonia or bacteremia due to other organisms and reported a test specificity of 97% (2/71 tests positive). In the study by Genne et al., 67 adults with